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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
POPA, ILEANA	
ART UNIT	PAPER NUMBER
1633	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/03/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/810,976	YOUNG ET AL.	
	Examiner	Art Unit	
	Ileana Popa	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 September 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11,15,18-25,29-47,68-73 and 76-80* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11,15,18-25,29-47,68-73 and 76-80* is/are rejected.

7)☒ Claim(s) *36-41, 76, and 77* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 09/21/2006 has been entered.

2. Claims 12-14, 16, 17, 26-28, 48-67, 74, and 75 have been cancelled. Claims 1, 10, 24, 36, 38, 40, and 76-80 have been amended.

Claims 1-11, 15, 18-25, 29-47, 68-73, and 76-80 are pending and under examination.

Note: Change of Examiner

The Examiner of record is now Ileana Popa, Art Unit 1633. Therefore, future correspondence should reflect such changes. Also, at the end of the Action is the information regarding the SPE and the Art Unit.

Double Patenting

3. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the

"right to exclude" granted by a patent and to prevent possible harassment by multiple assignees.

A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

4. Claims 1-11,15, 18-25, 29-47, and 76, 77, 79, and 80 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 7-10, 13-16, 19-21, and 23-25 of copending Application No. 10/660,893. Although the conflicting claims are not identical, they are not patentably distinct from each other because they are obvious variants.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

The instant claims are drawn to a method of elucidating a RNA transcription profile in a eukaryotic cell Serial Analysis of Vector integration (SAVI) (claims 1, 2, 36, 37, 76, 77, and 79), 5'SAVI (claims 10, 11, 38, 39, and

78), or 3'SAVI (claims 24, 25, 40, 41, and 80). SAVI uses a marker exon flanked by a 5' acceptor and a 3' splice donor sequence, wherein the marker exon comprises two different 5' restriction enzyme recognition (RER) sites and two different 3' RER sites and wherein one of each 5' and 3' RER are recognized by Type II restriction enzymes. 5' and 3'SAVI both use either the same marker exon; alternately, 5'SAVI uses a construct comprising in a 5' to 3' orientation a splice acceptor sequence a Type II RER site, a RER site, a marker exon, and a polyadenylation sequence (claim 78) and 3'SAVI uses a marker exon flanked by a 5' splice acceptor and a 3' splice donor sequence, wherein the marker exon contains at least two RER sites at the 3' end with one site being recognized by a Type II restriction enzyme (claim 80). The marker exon is contained in a viral vector (claims 3-6, 15, 18-20, and 29-32), the marker exon encodes GFP (claims 6-8, 21, 22, 33, and 34), and GFP is detected by flow cytometry (claim 9, 23, and 35), the marker exon is introduced into cells by transfection (claims 42-47). The specification discloses that GFP is humanized renilla GFP (p. 3, paragraph 0022).

The application claims recite a method of elucidating a protein expression profile in a cell by SAVI (claims 1, 7, 8, and 23), 5'SAVI (claims 9 and 24), or 3"SAVI (claims 10 and 25), wherein SAVI, 5'SAVI, and 3'SAVI use constructs identical to the claimed constructs, i.e., an oligonucleotide sequence encoding an assayable marker peptide (i.e., a marker exon) flanked by a 5' splice acceptor and a 3' splice donor sequence, wherein the oligonucleotide contains 5' and 3' Type II enzyme RER sites. The oligonucleotide encodes for humanized renilla

GFP (claims 14-16), the oligonucleotide can be introduced into the cell via a viral vector (claims 19-21), and GFP is detected by low cytometry (claim 13). The specification discloses that the marker oligonucleotide is introduced into cells by transfection (p. 8, paragraph 0077 and p. 10, paragraph 0095) and that the marker oligonucleotide contains non-Type II RER sites at both the 5' and the 3' ends (p. 5, paragraph 0044, p. 19, paragraph 0192). The specification also discloses that a polyadenylation sequence may be present downstream of the marker oligonucleotide and that for 3'SAVI the restriction sites are incorporated at the 3' end of the marker oligonucleotide (p. 5, paragraph 0043, p. 24, paragraph 0224). Thus, the application claims 1, 7-10, 13-16, 19-21, and 23-25 anticipate the instant claims 1-11,15, 18-25, 29-47, and 76, 77, 79, and 80. Since the claim of the Application No. 10/660,893 embrace all limitation of the instant claims, the application claims and the instant claims are obvious variants of one another.

5. Applicant is advised that should claims 1 and 2 be found allowable, claims 36, 37, 76, and 77 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. Should claims 10 and 11 be found allowable, claims 38 and 39 will be objected to as being a substantial duplicate thereof. Should claims 24 and 25 be found allowable, claims 40 and 41 will be objected to as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the

other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claim Rejections - 35 USC § 112, 2nd paragraph

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter that the applicant regards as his invention.

7. Claim 78 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. It is not clear whether "inverted conformation" means that the tag is cloned in the antisense orientation or whether the method comprises obtaining two tags in opposing orientation followed by their cloning. In the latter case, it is not clear how the pair of tags in opposing orientation is obtained. Since the metes and bounds of the claim cannot be determined, the claim is indefinite.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 70, 71, and 78 are rejected under 35 U.S.C. 103(a) as being obvious over Link et al. (U.S. Patent No. 6,897,020).

** The rejection is based upon interpretation of the claim as reciting cloning of the fragment tag in antisense orientation.

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). This rejection might also be overcome by showing that the reference is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(l)(1) and § 706.02(l)(2).

Link et al. teach a method of elucidating a protein expression profile in a cell by introducing into the genome of a cell a polynucleotide construct comprising in a 5' to 3' orientation a splice acceptor consensus sequence, a Type II RER site, an oligonucleotide sequence encoding an assayable marker peptide (i.e., a marker exon), and a polyadenylation sequence, wherein the expression of the marker exon occurs only after integration in an actively expressed gene (i.e.,

actively transcribed genome region) (claims 70 and 78), wherein the construct is part of a vector (claim 71). After the introduction of the construct, the expression profile is determined by SAVI, wherein SAVI is performed by: (i) isolating the mRNA from the cell, reverse transcribing the isolated mRNA into double-stranded (ds) cDNA (obtaining ds cDNA takes place by reverse transcribing the isolated mRNA into single-stranded (ss) DNA, extending the ssDNA with a homopolymeric polydeoxynucelotide sequence using a single a single deoxynucleotide triphosphate and a terminal transferase and synthesizing the second strand using a DNA polymerase and a primer complementary to the homopolymeric sequence), (ii) subjecting the cDNA to digestion with a Type II restriction enzyme that recognizes the 5' Type II RER site and cleaving the cDNA upstream of the marker exon, producing a cDNA fragment comprising the marker exon and portions of upstream cellular exon tag (it is noted that, since a Type II restriction enzyme is used, the cellular exon tags must necessarily have 5' single-stranded overhangs), (iii) adding an adaptor (i.e., a linker) to the digested cDNA fragment (since the exon tag has have 5' single-stranded overhangs, the adaptor must necessarily have 3' single-stranded overhangs complementary and ligatable to the 5' single-stranded overhangs of the exon tags), (iv) amplifying the cDNA fragments with primers complementary to the marker exon and ligated adaptor, (v) cloning and sequencing the amplified fragments, and (vi) comparing the sequence of each fragment to one or more nucleotide databases such that the protein corresponding to the sequenced tag is identified (claims 70 and 78) (Fig. 17A, column 7, lines 45-66, claims 1, 3, 4, and 20-22). Link et al. teach that

the database can consist of annotated or un-annotated genomic sequences expressed in cells as RNA, therefore they teach identifying the RNA transcript corresponding to the sequenced tag (column 33, lines 6-21). Link et al. do not specifically teach a RER site located downstream of the Type II RER site, wherein the RER site is not recognized by the previously used Type II restriction enzyme and wherein the used for cutting and cloning the sequence tags. However, it would have been obvious to one of skill in the art, at the time the invention was made, to introduce this additional RER site, with a reasonable expectation of success. One of skill in the art would have been motivated to do so in order to provide facile tag sequencing and identification. One of skill in the art would have been expected to have a reasonable expectation of success because the art teaches that such sites can be successfully introduced into any construct. Additionally, one of skill in the art would have known to clone the tags in either sense or antisense orientation, depending on the primers used. Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

10. Claims 1-6, 36, 37, 42, 43, 68, 69, 76, 77, and 79 are rejected under 35 U.S.C. 103(a) as being obvious over Jarvik et al. (Biotechniques, 1996, 20: 896-904), in view of each Smith (Biotechniques, 1997, 23: 116-120), Velculescu et al. (Science, 1995, 270: 484-487), and the 1996 New England Biolabs, Inc. Catalog (p. 39).

Jarvik et al. teach a method of tagging genes and proteins by introducing into a cell a polynucleotide construct comprising a short open reading frame flanked by 5' splice acceptor and 3' splice donor sequences (the CD cassette), wherein the CD is introduced into the introns of target genes and is expressed only when the target gene is transcribed (claims 1, 36, 42, 68, 76, 77, and 79) and wherein the CD cassette is part of a retroviral vector (claims 3-6 and 69) or can be introduced into cells by transfection (claims 42 and 43) (Abstract, p. 896, column 2, p. 903, column 3). Jarvik et al. teach that CD-tagging can be used to analyze the genes, transcripts, and proteins and also cloning and sequencing of the tagged transcripts by using the unique nucleotide tags and RT-PCR (i.e., Jarvik et al. teach a method of elucidating the transcriptional profile in a cell) (Abstract, p. 903, column 3). Jarvik et al. do not teach Type II RER sites (claims 1, 1, 36, 42, 68, 76, and 77). Smith teaches a mini-exon comprising in a 5' to 3' orientation: (i) a splice acceptor sequence, (ii) the sequence GAGG, a sequence complementary to the *Mnl* I Type IIS RER sequence, (iii) an oligonucleotide encoding a myc epitope that does not have stop codons in any of the reading frames (i.e., a marker exon), (iv) the sequence CCTC, a *Mnl* I Type IIS RER sequence, and (v) a splice donor sequence (Fig. 1, p. 117 bridging p. 118). The 1996 New England Biolabs Catalog is cited only to show that the recognition sequence for *Mnl* I is 5'-CCTCNNNNNNN-3'. Smith teaches their method as a tool for gene discovery by randomly inserting the mini-exon into introns using retroviruses, wherein the method permits gene products detection using the same tags regardless of intron class (p. 116, column 2, first paragraph, p. 119,

column 1, second full paragraph). Smith teaches their method as being simple, rapid, and amenable to automation (p. 1198, column 1, second full paragraph, column 2). Smith also teaches comparing the sequenced tags to nucleic acid databases to identify the transcripts (p. 485, column 3, p. 486, column 1). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the method of Jarvik et al. by replacing their open reading frame with the mini-exon of Smith, with a reasonable expectation of success. The motivation to do so is provided by Smith, who teaches that, although the two methods are conceptually similar, CD-tagging has the disadvantage of using three different vectors (i.e., three different tags) to solve the problem of the three different reading frames by which an intron can interrupt a gene, whereas using a mini-exon has the advantage of being more rapid, since only one tag is used regardless of the intron used (p. 119, column 2). One of skill in the art would have been expected to have a reasonable expectation of success in doing so because the art teaches the successful use of mini-exons in gene analysis. Neither Jarvik et al., nor Smith teach (i) subjecting the RT-PCR product (i.e., double stranded cDNA) to digestion with a Type IIS restriction enzyme that recognize the 5' Type IIS RER site and a Type IIS restriction enzyme that recognize the 3' Type IIS RER site, (ii) blunt-ending the cDNA fragment thus obtained, (iii) self-ligating the cDNA fragment to fuse the exon tags in opposing orientation, (iv) amplifying the region of cDNA fragment containing the exon tags in opposing orientation to obtain a linear DNA molecule containing the exon tags in opposing orientation flanked by sequences corresponding to the marker exon

5' and 3' ends, (v) digesting the linear DNA with restriction enzymes recognizing RER sites not recognized by the Type IIS restriction enzymes, generating a linear DNA fragment containing upstream and downstream exon tags fused in an inverted orientation, and (vi) cloning the fragment (claims 1, 1, 36, 42, 68, 76, and 77). However, Velculescu et al. teach all these steps (p. 484, column 3, p. 485, columns 1 and 2, p. 486, columns 1 and 2). Velculescu et al. also teach ligating the amplified fragments to form a concatamer before cloning (claims 2 and 37) (p. 485, column 2). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the method of Jarvik et al. and Smith by further including the cloning and sequencing steps taught by Velculescu et al., with a reasonable expectation of success. The motivation to do so is provided by Velculescu et al., who teach that analysis of ditags before any amplification eliminates potential distortions introduced by PCR. The motivation to form concatamers is also provided by Velculescu et al., who teach that tag concatenation allows the efficient analysis of transcripts in a serial manner by sequencing multiple tags within a single clone (p. 484, column 1, second paragraph). Jarvik et al. taken Smith do not teach second 5' and 3' RER sites (claims 1, 1, 36, 42, 68, 76, and 77). However, it would have been obvious to one of skill in the art, at the time the invention was made, to introduce these additional RER sites, with a reasonable expectation of success. One of skill in the art would have been motivated to do so in order to provide facile tag sequencing and identification. It is also noted that Velculescu et al. teach cleaving the PCR product to isolate the ditags before concatenation and cloning

(p. 485, column 2). One of skill in the art would have been expected to have a reasonable expectation of success because the art teaches that such sites can be successfully introduced into any construct. With respect to the specific arrangements of RER sites recited in the instant claims, it is noted that there is no evidence on the record that the claimed arrangements result in a construct exhibiting an unexpected property. The arrangement is not significant if it does not provide a novel feature. Moreover, it would have been obvious to the ordinary skilled artisan to vary the arrangement, with the purpose to achieve the optimum results. Absent evidence to the contrary, it is generally not inventive to discover the optimal working conditions of a prior art method, such conditions can be identified by routine experimentation. With respect to the limitation that the restriction recognition sites be located close from the border of the marker exon such that after cutting flanking exons generate tags of 8-20 nucleotides (claim 79), this is not innovative over the prior art; Velculescu et al. teach that Type IIS restriction enzymes cut up to 20bp away from the asymmetric recognition sites and that the sites are designed to produce the release of short exon tags (p. 484, column 2). Given these teachings, one of skill in the art would have known to engineer these sites such as to generate the claimed tags after cutting. Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

11. Claims 1-9, 36, 37, 42, 43, 68, 69, 76, 77, and 79 are rejected under 35 U.S.C. 103(a) as being obvious over Jarvik et al. taken with Smith, Velculescu et

al., and the New England Biolabs, Inc. Catalog, as applied to claims 1-6, 36, 37, 42, 43, 68, 69, 76, 77, and 79, in further view of Morin et al. (Proc Natl Acad Sci USA, 2001, 98: 15050-15055).

Although Jarvik et al. teach screening of tagged proteins by flow cytometry (claim 9) (p. 903, column 2), they do not specifically teach GFP. Therefore, Jarvik et al. taken with Smith and Velculescu et al. do not teach GFP (claims 7 and 8). Morin et al. teach a gene trap strategy using an artificial exon encoding GFP, wherein the exon does not have initiation and stop codons and wherein the exon is flanked by 5' splice acceptor and 3' splice donor sequences (p. 15050, column 2, second paragraph, Fig. 1). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the method of Jarvik et al., Smith, and Velculescu et al. by replacing the mini-exon of Smith with the exon of Morin et al., with a reasonable expectation of success. The motivation to do so is provided by Morin et al., who teach that GFP allows the determination of the subcellular localization of the endogenous proteins (p. 15050, column 2, p. 15051, column 2). Moreover, the art teaches the use of GFP in flow cytometry and since Jarvik et al. teach screening by flow cytometry, one of skill in the art would have been motivated to use GFP for the additional benefit of detecting and measuring the tagged proteins and also fore separating the cells expressing the GFP tags. One of skill in the art would have been expected to have a reasonable expectation of success in doing such because the art teaches the successful use of artificial GFP exon for analysis of gene expression. Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

12. Claims 10, 15, 18-20, 38, and 44 are rejected under 35 U.S.C. 103(a) as being obvious over Jarvik et al., in view of each Smith, Townley et al. (Genome Research, 1997, 7: 293-298), and the New England Biolabs, Inc. Catalog.

The teachings of Jarvik et al. taken with Smith and New England Biolabs, Inc. Catalog are applied in the instant rejection as described above. Neither Jarvik et al., nor Smith specifically teach (i) obtaining a ss cDNA using a primer sequence complementary to the marker exon, (ii) extending the 3'-end of the ss cDNA with a homopolymeric polydeoxynucleotide using a single deoxynucleotide triphoshpate and a terminal transferase, (iii) synthesizing a second and complementary cDNA using a primer complementary to the homopolymeric sequence, (iv) subjecting the ds cDNA to a Type IIS restriction enzyme that recognizes the 5'-end Type IIS RER site, (v) ligating a linker to the 5'-end of the cut fragment, (vi) amplifying the linker and the cDNA fragment with primers complementary to the marker exon and the ligated linker, (vii) cleaving the amplified product with a restriction enzyme that recognizes the RER site not recognized by the Type IIS restriction enzyme, and (viii) cloning the fragment. However, Townley et al. teach these steps (p. 727, column 1). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the method of Jarvik et al. and Smith by further including the cloning and sequencing steps taught by Townley et al., with a reasonable expectation of success. The motivation to do so is provided by Townley et al., who teach the utility of their method in genetic screens for the rapid identification of 5' sequence of transcripts (Abstract, p. 726, column 1). Although Townley et al. do not teach

cutting with a Type IIS restriction enzyme, one of skill in the art would have known and motivated to use this site to obtain a shorter fragment containing 5' tag that can be easily sequenced. Jarvik et al. taken Smith do not teach second 5' and 3' RER sites (claims 10 and 38). However, it would have been obvious to one of skill in the art, at the time the invention was made, to introduce these additional RER sites, with a reasonable expectation of success. One of skill in the art would have been motivated to do so in order to provide facile tag sequencing and identification. One of skill in the art would have been expected to have a reasonable expectation of success because the art teaches that such sites can be successfully introduced into any construct. With respect to the limitation of cloning the amplified fragments, this is not innovative over the prior art. One of skill in the art would have known to clone the amplified fragments to provide sequencing primer sites. Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

13. Claims 10, 11, 15, 18-20, 38, 39, 44, and 45 are rejected under 35 U.S.C. 103(a) as being obvious over Jarvik et al. taken with Smith, Townley et al., and the New England Biolabs, Inc. Catalog, as applied to claims 10, 15, 18-20, 38, and 44, in further view of Velculesu et al.

Jarvik et al. taken with Smith, Townley et al. do not teach forming concatamers before cloning (claims 11, 39, and 45). Velculescu et al. also teach obtaining concatamers before cloning (p. 485, column 2). It would have been obvious to one of skill in the art, at the time the invention was made to obtain

concatamers before cloning, with a reasonable expectation of success. The motivation to do so is provided by Velculescu et al., who teach that tag concatenation allows the efficient analysis of transcripts in a serial manner by sequencing multiple tags within a single clone (p. 484, column 1, second paragraph). One of skill in the art would have been expected to have a reasonable expectation of success in doing such because the art teaches that concatamers can be successfully obtained and cloned. Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

14. Claims 10, 15, 18-23, 38, 44, and 45 are rejected under 35 U.S.C. 103(a) as being obvious over Jarvik et al. taken with Smith, Townley et al., and the New England Biolabs, Inc. Catalog, as applied to claims 10, 15, 18-20, 38, 44, and 45, in further view of Morin et al.

Although Jarvik et al. teach screening of tagged proteins by flow cytometry (claim 23) (p. 903, column 2), they do not specifically teach GFP. Therefore, Jarvik et al. taken with Smith and Townley et al. do not teach GFP (claims 21 and 22). Morin et al. teach a gene trap strategy using an artificial exon encoding GFP, wherein the exon does not have initiation and stop codons and wherein the exon is flanked by 5' splice acceptor and 3' splice donor sequences (p. 15050, column 2, second paragraph, Fig. 1). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the method of Jarvik et al., Smith, and Townley et al. by replacing the mini-exon of Smith with the exon of Morin et al., with a reasonable expectation of success. The motivation to do

so is provided by Morin et al., who teach that GFP allows the determination of the subcellular localization of the endogenous proteins (p. 15050, column 2, p. 15051, column 2). Moreover, the art teaches the use of GFP in flow cytometry and since Jarvik et al. teach screening by flow cytometry, one of skill in the art would have been motivated to use GFP for the additional benefit of detecting and measuring the tagged proteins and also fore separating the cells expressing the GFP tags. One of skill in the art would have been expected to have a reasonable expectation of success in doing such because the art teaches the successful use of artificial GFP exon for analysis of gene expression. Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

15. Claims 24, 29-32, 40, 46, 72, 73, and 80 are rejected under 35 U.S.C. 103(a) as being obvious over Jarvik et al., in view of each Smith, Townley et al., and the New England Biolabs, Inc. Catalog.

The teachings of Jarvik et al. taken with Smith and New England Biolabs, Inc. Catalog are applied in the instant rejection as described above. It is noted that the construct of Jarvik et al. taken with Smith and New England Biolabs, Inc. Catalog meets the limitation recited in claim 72. Neither Jarvik et al., nor Smith specifically teach (i) synthesizing a ss cDNA and a second complementary strand of cDNAusing a primer whose sequence corresponds to the sequence of the marker exon, (ii) digesting the ds cDNA with a Type IIS enzyme that recognizes the 3' Type IIS RER site, (iii) ligating a linker to the ligating a linker to the 3'-end of the cut fragment, (vi) amplifying the linker and the cDNA fragment with primers

complementary to the marker exon and the ligated linker, (vii) cleaving the amplified product with a restriction enzyme that recognizes the RER site not recognized by the Type IIS restriction enzyme, and (viii) cloning the fragment. However, Townley et al. teach these steps (see above). Although Townley et al. do not specifically teach identification of the 3' sequence tag, one of skill in the art would have known that their method could also be applied for the identification of the 3' tag and therefore, it would have obvious to one of skill in the art, at the time the invention was made, to modify the method of Jarvik et al., Smith, and Townley et al. by cleaving the ds cDNA with the Type IIS restriction enzyme recognizing the 3' Type IIS RER site, with a reasonable expectation of success. As noted above, although Townley et al. do not teach cutting with a Type IIS restriction enzyme, one of skill in the art would have known and motivated to use this site to obtain a shorter fragment containing 3' tag that can be easily sequenced. Regarding the second restriction sites, see above. One of skill in the art would have been expected to have a reasonable expectation of success in doing such because the art teaches the successful use of such methods for exon tag sequencing and identification. With respect to the limitation of cloning the amplified fragments, this is not innovative over the prior art. One of skill in the art would have known to clone the amplified fragments to provide sequencing primer sites. Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

16. Claims 24, 25, 29-32, 40, 41, 46, 47, 72, 73, and 80 are rejected under 35 U.S.C. 103(a) as being obvious over Jarvik et al. taken with Smith, Townley et al., and the New England Biolabs, Inc. Catalog, as applied to claims 24, 29-32, 40, 46, 72, 73, and 80 above, in further view of Velculesu et al.

Jarvik et al. taken with Smith, Townley et al. do not teach forming concatamers before cloning (claims 25, 41, and 47). Velculescu et al. also teach obtaining concatamers before cloning (p. 485, column 2). It would have been obvious to one of skill in the art, at the time the invention was made to obtain concatamers before cloning, with a reasonable expectation of success. The motivation to do so is provided by Velculescu et al., who teach that tag concatenation allows the efficient analysis of transcripts in a serial manner by sequencing multiple tags within a single clone (p. 484, column 1, second paragraph). One of skill in the art would have been expected to have a reasonable expectation of success in doing such because the art teaches that concatamers can be successfully obtained and cloned. Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

17. Claims 24, 29-35, 40, 46, 72, 73, and 80 are rejected under 35 U.S.C. 103(a) as being obvious over Jarvik et al. taken with Smith, Townley et al., and the New England Biolabs, Inc. Catalog, as applied to claims 24, 29-32, 40, 46, 72, 73, and 80 above, in further view Morin et al.

Although Jarvik et al. teach screening of tagged proteins by flow cytometry (claim 35) (p. 903, column 2), they do not specifically teach GFP. Therefore,

Jarvik et al. taken with Smith and Townley et al. do not teach GFP (claims 33 and 34). Morin et al. teach a gene trap strategy using an artificial exon encoding GFP, wherein the exon does not have initiation and stop codons and wherein the exon is flanked by 5' splice acceptor and 3' splice donor sequences (p. 15050, column 2, second paragraph, Fig. 1). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the method of Jarvik et al., Smith, and Townley et al. by replacing the mini-exon of Smith with the exon of Morin et al., with a reasonable expectation of success. The motivation to do so is provided by Morin et al., who teach that GFP allows the determination of the subcellular localization of the endogenous proteins (p. 15050, column 2, p. 15051, column 2). Moreover, the art teaches the use of GFP in flow cytometry and since Jarvik et al. teach screening by flow cytometry, one of skill in the art would have been motivated to use GFP for the additional benefit of detecting and measuring the tagged proteins and also fore separating the cells expressing the GFP tags. One of skill in the art would have been expected to have a reasonable expectation of success in doing such because the art teaches the successful use of artificial GFP exon for analysis of gene expression. Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

18. No claim is allowed. No claim is free of prior art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ileana Popa whose telephone number is 571-272-5546. The examiner can normally be reached on 9:00 am-5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Ileana Popa, PhD